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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,957	01/26/2004	James McSwiggen	02-742-O (400.144)	9923
20306	7590	02/21/2006	EXAMINER	
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP 300 S. WACKER DRIVE 32ND FLOOR CHICAGO, IL 60606			GIBBS, TERRA C	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 02/21/2006.

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/764,957

Applicant(s)

MCSWIGGEN ET AL.

Examiner

Terra C. Gibbs

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 October 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 1/26/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/13/05 & 7/22/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a response to Applicant's Preliminary Amendment filed October 12, 2004.

Claims 1-33 are pending in the instant application.

Claims 1-33 have been examined on the merits.

Information Disclosure Statement

Applicant's information disclosure statement filed October 13, 2005 is acknowledged. The submission is not fully compliant with the provisions of 37 CFR §1.97, which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It is noted that an English translation of Document Number 2, Japanese Document 08208687, has not been provided. Therefore, Document Number 2 has not been considered on the merits. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith, however Document Number 2 has been lined through, indicating that the reference has not been considered.

Applicant's information disclosure statement filed July 22, 2004 is acknowledged. The submission is not fully compliant with the provisions of 37 CFR §1.97, which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It is noted that an English translation of Document

Art Unit: 1635

Numbers 3, 21, 39, 43, 65, and 66, EP Document Number 1144623, WO Document Number 99/14226, WO Document Number 01/42443, WO Document Number 01/70944, WO Document Number 03/030989, and WO Document Number 03/043689, respectively, have not been provided. Therefore, Document Numbers 3, 21, 39, 43, 65, and 66 have not been considered on the merits. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith, however Document Numbers 3, 21, 39, 43, 65, and 66 have been lined through, indicating that these references have not been considered.

Priority

Applicant's reference to priority in the first sentence of the specification is acknowledged, however the reference should be updated to reflect applications for patents that have been abandoned.

It is noted that the instant application has been afforded priority to September 16, 2003, which is the filing date of USSN 10/665,255 because support for the terms "about 19 to about 21 base pairs" as recited in claims 1-30 and 33, or "about 21 nucleotides" as recited in claims 31 and 32, is not found in any of the later filed parent applications for which Applicants claim benefit.

In summary, support for the terms "about 19 to about 21 base pairs" and "about 21 nucleotides" is found in parent Application 10/665,255, but not in any other later filed parent application(s) that Applicants claim priority to. Therefore the instant claims have been afforded priority to September 16, 2003, which is the filing date of parent

Art Unit: 1635

Application 10/665,255.

Claim Objections

Claims 18 and 31 are objected to because of the following informalities:

Claim 18 is missing a period at the end of the claim. Appropriate correction is required.

Claim 31 contains a typographical error since it appears that the word "comprisess" should be correctly spelled as "comprises". Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-33 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-30 of copending Application No. US Publication No. 20040209832 ('832). This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Art Unit: 1635

Claims 1-33 of the instant application are drawn to a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a vascular endothelial growth factor (VEGF) gene, wherein said siNA molecule comprises about 19 to about 21 base pairs. Claims 1-30 of copending Application No. '832 are drawn to a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a vascular endothelial growth factor (VEGF) gene, wherein said siNA molecule comprises about 19 to about 21 base pairs, wherein each strand of said siNA molecules comprises one or more chemical modifications.

Claims 1-30 of co-pending application '832 embraces the double-stranded short interfering nucleic acid (siNA) as instantly claimed and thus fully encompasses the subject matter of the instant application.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Art Unit: 1635

The subject matter of the instantly claimed invention is drawn to a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a vascular endothelial growth factor (VEGF) gene, wherein said siNA molecule comprises about 19 to about 21 base pairs.

The specification teaches a series of VEGF siNA and target sequences to human VEGF (Genbank Accession No. NM_003376.3). However, the specification and the prior art also teach dozens of different VEGF genes (see, for example, Genbank Accession Nos. listed at pages 150-153 of the instant specification and GenBank Accession Nos. U48801 and U52819, for example). Neither the instant specification, nor the prior art describe siNA molecules targeted to other VEGF genes, other than Genbank Accession No. NM_003376.3.

At the outset it is noted that the rejected claims do not recite any sequence identifier relating to a VEGF gene. This sequence is thus considered to be defined by its function (i.e. the activity of a VEGF gene) rather than by any one specific structure. Accordingly, the claims embrace siNA molecules that down-regulates expression of any sequence of any VEGF gene, or any such molecule with analogous VEGF gene activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain VEGF gene activity.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of

Art Unit: 1635

filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, Figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, Figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was

Art Unit: 1635

“ready for patenting” such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention.

Further, See MPEP § 2163, which states “[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.”

In order to synthesize the siNA molecules that down-regulates expression of a VEGF gene, one of skill would first need the sequence of the VEGF gene in order to synthesize said siNA. However, one of skill in the art could not immediately envision the genus of said siNA molecules that down-regulates expression of a VEGF gene from the disclosure of a series of siNA molecules targeted to only one such sequence, particularly in the absence of any teaching by way of structure or reference to active domains or regions. The genus is not immediately envisioned because the genus of siNA molecules is considered to include not only the VEGF sequence of Genbank Accession No. NM_003376.3 as taught in the instant specification, but also any such molecule with analogous VEGF activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain VEGF activity. However, the distinguishing characteristics of the claimed genus are not

Art Unit: 1635

considered to be described herein, or in the prior art. Thus, because one of skill in the art could not envision any siNA molecules that down-regulates expression of a VEGF gene, other than Genbank Accession No. NM_003376.3, one of skill would not be convinced that applicants were in possession of any siNA molecules that down-regulates expression of a VEGF gene sequences that are heretofore undescribed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-9, 23, and 31-33 are rejected under 35 U.S.C. 102(a) as being anticipated by Reich et al. (Molecular Vision, 2003 Vol. 9:210-216, Applicant's Document No. 256 on the information disclosure statement filed July 22, 2004).

The instant invention is drawn to a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a vascular endothelial growth factor (VEGF) gene, wherein said siNA molecule comprises about 19 to about 21 base pairs.

Reich et al. disclose small interfering RNA (siRNA) targeting VEGF effectively inhibits ocular neovascularization in a mouse model (see Abstract). Reich et al. disclose siRNA duplexes consisting of a sense and antisense strand targeted to mouse and human VEGF (see page 211, first column, first paragraph). Reich et al. also

Art Unit: 1635

disclose RNA interference significantly diminishes levels of human VEGF protein expression *in vivo* (see Figure 3). Reich et al. also disclose siRNA were administered with a transfection reagent and thus constitutes a pharmaceutically acceptable carrier or diluent.

Therefore, Reich et al. anticipate claims 1, 3-9, 23, and 31-33.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reich et al. (Molecular Vision, 2003 Vol. 9:210-216, Applicant's Document No. 256 on the information disclosure statement filed July 22, 2004), in view of Parrish et al. (Molecular Cell, Vol. 6, pp. 1077-1087, 2000, Applicant's Document No. 246 on the information disclosure statement filed July 22, 2004), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001, Applicant's Document Number 114 on the information disclosure statement filed July 22, 2004), Cook et al. (US 5,587,471), and Schmidt et al. (Nucleic Acids Research, 1996, Vol. 24, No. 4, pages 573-581).

The instant invention is drawn to a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a vascular endothelial growth factor

Art Unit: 1635

(VEGF) gene, wherein said siNA molecule comprises about 19 to about 21 base pairs. The invention is further drawn to modifications to the siNA molecule, as well as to a composition comprising the siNA molecule and a pharmaceutically acceptable carrier or diluent.

Reich et al. teach a specific nucleic acid inhibitor of gene expression, small interfering RNA (siRNA). Reich et al. teach siRNA targeting VEGF effectively inhibits ocular neovascularization in a mouse model (see Abstract). Reich et al. teach siRNA duplexes consisting of a sense and antisense strand targeted to mouse and human VEGF (see page 211, first column, first paragraph). Reich et al. also teach RNA interference significantly diminishes levels of human VEGF protein expression *in vivo* (see Figure 3).

Reich et al. do not teach wherein the short interfering molecule comprises modifications.

Parrish et al. teach modified double stranded siNA molecules as nucleic acid inhibitors of gene expression, which comprise a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence. It is noted that one or both strands comprise modifications. Each strand of the siNA molecules taught by Parrish et al. comprises about 21 nucleotides, more specifically 26 nucleotides. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the interference process (see summary). Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense

Art Unit: 1635

or antisense strand (see Figure 5). The assays carried out by Parrish et al. utilize pharmaceutically acceptable diluents, such as water.

Elbashir et al. teach dsRNA duplexes as nucleic acid inhibitors, which consist of 21-23 nucleotides in length with 2 nt or 3' overhangs. Elbashir et al. teach 2'-deoxy and 2'-O-methyl modifications to one or both strands. Elbashir et al. teach that modifications are tolerated depending on the location in the duplex. Elbashir et al. teach that substitution of the 2 nt 3' overhangs by 2'-deoxynucleotides had no effect and even the replacement by two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Elbashir et al. teach 2'-deoxythymidines. Elbashir et al. teach an embodiment wherein the siRNA is blunt ended with 21 nucleotides base paired between duplex strands (see Figure 1F). Elbashir et al. teach complete substitution of one or both strands of the siRNA duplex, wherein the completely substituted duplex is considered to comprise no ribonucleotides. Elbashir et al. teach that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function.

Cook et al. teach various conjugates and modifications that can be incorporated into oligonucleotide inhibitors to improve the pharmacokinetic properties of an oligonucleotide, including glyceryl (see columns 2 and 3).

Schmidt et al. teach hairpin RNA nucleic acid inhibitor comprising a sense and antisense region connected via a polynucleotide or non-polynucleotide linker (see Figure 3). Schmidt et al. teach that linkers increase hairpin RNA cleavage efficiencies (see page 575).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a double-stranded siNA molecule that down-regulates expression of a VEGF gene since Reich et al. explicitly teach such a molecule inhibits ocular neovascularization *in vivo*, which is important in treating retinal diseases. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the siNA molecule with 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al., 2'-O-methyl modifications, phosphorothioates, 2'-deoxy and 2'-O-methyl modifications to one or both strands, as well as 3' overhangs of 2'-deoxy-thymidines, as taught by Elbashir et al., as well as to incorporate polynucleotide or non-nucleotide linkers, as taught by Schmidt et al., and glyceryl modifications, as taught by Cook et al., since the prior art taught such modifications protect the nucleic acid molecule from nuclease degradation.

One of ordinary skill in the art would have been motivated to incorporate each of the above-mentioned modifications with a siNA molecule that down-regulates expression of a VEGF gene since each of the modifications were known to enhance the activity and increase resistance to nucleases of nucleic acid specific inhibitors of target gene expression. The modifications were each known in the art, as evidenced by the modified siRNA duplexes taught by Elbashir et al. and Parrish et al., hairpins taught by Schmidt et al., and modified oligonucleotides taught by Cook et al. One would be motivated to maximize a double stranded nucleic acid by incorporating each of the modifications that were known in the art. Elbashir et al. and Parrish et al. each teach combinations of modifications to duplexes and teach that different modifications are

Art Unit: 1635

tolerated at different locations of the duplex. One of ordinary skill in the art would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a dsRNA duplex in order to optimize delivery of the duplex.

One of ordinary skill in the art would have a reasonable expectation of success of making a modified double-stranded siNA molecule that down-regulates expression of a VEGF gene given that each of the modifications were known in the art at the time the invention was made to add benefits to oligonucleotides, such as increasing resistance to nucleases. One of ordinary skill in the art would expect for such modifications to benefit siNA duplexes, as each had shown to benefit either siRNA duplexes or other antisense oligonucleotide inhibitors such as antisense oligonucleotides or ribozymes. One of ordinary skill in the art would reasonably expect for polynucleotide or non-nucleotide linkers as taught by Schmidt et al. to benefit the instant invention since such linkers were known in the art at the time the invention was made to increase cleavage efficiency.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

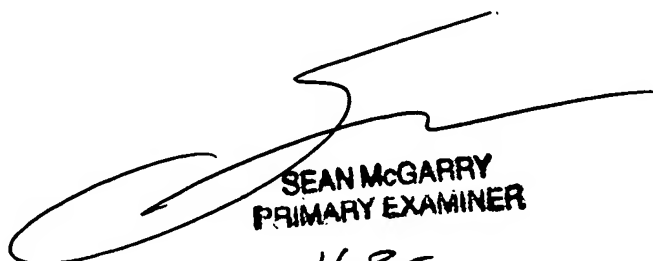
Art Unit: 1635

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
February 9, 2006



SEAN MCGARRY
PRIMARY EXAMINER
1635